

AN EVALUATION OF POTASSIUM IODIDE AS A THERAPEUTIC AGENT IN THE TREATMENT OF EXPERIMENTAL HYPERCHOLESTEREMIA AND ATHEROSCLEROSIS¹

BY MEYER FRIEDMAN, RICHARD HOMER,² AND SANFORD O. BYERS WITH THE TECHNICAL ASSISTANCE OF CLARENCE OMOTO AND WARREN HAYASHI

(From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco 15, Calif.)

(Submitted for publication March 19, 1956; accepted May 24, 1956)

Although iodides have been administered for many decades to patients suffering from arteriosclerotic disorders, it was Liebig (1, 2) who first furnished experimental data possibly justifying the use of this substance in such disorders. He observed that the majority of his cholesterol fed rabbits could be protected against subsequent aortic atherosclerosis if iodide were administered.

Since his initial observations, various other studies have been done concerning the possible protective effect of iodide administration against both experimentally induced hypercholesteremia and atherosclerosis. Some (3-6) have agreed with the conclusions of Liebig but others (7, 8) were unable to demonstrate any specific anti-hypercholesteremic or anti-atherogenic effect of iodide administration. Furthermore, although Turner (3) initially observed that iodide administration was protective, he and Bidwell (9, 10) later observed that at best the supposed protection by iodide administration was but a temporary phenomenon. Finally, Brown and Page (11) were unable to detect any effect of iodide administration upon the hepatic cholesterol content of the normal, cholesterol fed rabbit.

In view of these sometimes conflicting reports it was decided therefore to pursue a series of studies concerning the possible effects of iodide administration both upon normo- and hypercholesteremic animals with the intent of determining the actual efficacy of this cation both as an antihypercholesteremic and antiatherogenic agent. The results clearly indicate that iodide *per se* possesses neither of these two effects.

¹ Aided by Grants from the Life Insurance Medical Research Fund and the National Institutes of Health, Grant H-119 (C6), Public Health Service.

² Work done while Public Health Service Research Fellow, National Heart Institute, National Institutes of Health, HF-4788.

I. *The Effect of Potassium Iodide Upon Intestinal Absorption of Cholesterol*

Methods

A. *Rats*: A series of male Long-Evans rats (average weight: 235 to 251 grams) previously starved for 24 hours was given 25 mg. of cholesterol in 1.0 ml. of olive oil by stomach tube and then divided into four groups. Group I (17 rats) which served as a control received only the 25 mg. of cholesterol. Group II (9 rats) received in addition 25 mg. of KI with the cholesterol. Group III (8 rats) received 100 mg. of KI in addition to the cholesterol. Group IV (7 rats) received 200 mg. of KI plus the cholesterol. All of the animals then were anesthetized with ether, the abdomen incised, the intestinal lymph duct cannulated and the lymph collected for 24 hours by methods previously described (12). This collected lymph then was analyzed for total cholesterol by the method of Saifer and Kammerer (13) and for total lipid by the method of Bragdon (14).

B. *Rabbits*: A series of young male rabbits (average weight: 1,424 to 1,436 grams) was given 800 mg. of cholesterol dissolved in 8 ml. of olive oil by stomach tube and then divided into two groups. Group I (16 rabbits) which served as a control received only the cholesterol. Group II (10 rabbits) received in addition to the cholesterol, 1,250 mg. of KI. The animals then were caged individually and fed a cholesterol-free diet (leafy vegetables) for 72 hours. All feces excreted during this period were individually collected and analyzed for total sterol, total cholesterol, and non-cholesterol sterol according to methods previously described (12).

Results

Inspection of Tables I and II will indicate that the oral administration of potassium iodide had no significant effect upon the intestinal absorption of cholesterol in either the rat or the rabbit. Regardless of whether the rat was given 25, 100 or 200 mg. of KI, the total amount of cholesterol absorbed during the 24 hours following the ingestion of 25 mg. of cholesterol did not appear to differ from that observed in the control animals (*cf.* A with B, C and D of Table I). Similarly, no

TABLE I
The effect of KI on absorption of cholesterol and total lipid in the rat

No. of rats	Average weight gm.	Volume ml.	Lymph			
			Total cholesterol		Total lipid	
			mg./100 ml.	mg./24 hrs.	mg./100 ml.	mg./24 hrs.
A. Control rats given 25 mg. of cholesterol						
17	248 Range: (225-300) S.E. Mean:	29.6 (21.5-43.5)	66 (38-106)	18.6 (13.0-28.0) ±0.9	1,974 (1,230-3,290)	560 (320-990) ±37
B. Rats given 25 mg. of cholesterol + 25 mg. of KI						
9	241 Range: (234-255) S.E. Mean:	31.7 (23-45.5)	58 (44-92)	17.6 (12.0-24) ±1.3	1,948 (1,000-2,960)	514 (270-930) ±65
C. Rats given 25 mg. of cholesterol + 100 mg. of KI						
8	235 Range: (210-278) S.E. Mean:	41.0 (29-52)	52 (37-61)	20.6 (17.5-24.8) ±0.9	2,043 (1,315-3,950)	793 (510-1,190) ±91
D. Rats given 25 mg. of cholesterol + 200 mg. of KI						
7	251 Range: (226-274) S.E. Mean:	29.8 (23-38)	57 (46-71)	17.1 (14.0-22.0) ±1.3	1,783 (1,543-2,300)	529 (365-600) ±35

effect of KI administration upon the absorption of total lipid was observed.

Similarly in the rabbits, whether one employs the total sterol or the total cholesterol contents of the 72-hour intestinal excretion as an indicator, no significant difference was found in the excretion of cholesterol in the rabbit fed KI in addition to the 800 mg. of cholesterol. This similarity in the excretion of total sterol and cholesterol in the two groups of course implies that a similarity in the amount of ingested cholesterol absorbed must also have existed.

II. The Effect of Potassium Iodide Upon Intestinal Excretion of Cholesterol

Methods

This function was studied in the rat. A group of 10 male Long-Evans rats (average weight: 233 to 248 grams) was given 3 ml. of olive oil and then half of the rats were given 200 mg. of KI. The animals then were individually caged, given a sterol-free diet and the feces were collected for 72 hours and analyzed for total sterol, total cholesterol and non-cholesterol sterol as done above.

Results

The ingestion of KI did not appear to influence the intestinal excretion of cholesterol. Thus (see

Table III) the total sterol and cholesterol excretion of the control rats was 29.8 and 15.1 mg., respectively, as compared to 32.3 and 12.9 mg., respectively, in the rats given KI. Calculation of the Standard Error of the Difference of Means indicates good agreement between these sets of values.

III. The Acute and Chronic Effect of Potassium Iodide Upon Plasma Cholesterol and Total Lipid

Methods

A. Rats: The acute effect of KI upon the plasma cholesterol and total lipid of the rats was studied by giving one series of rats a stock diet of Purina laboratory chow and a second series, the same diet enriched with cholesterol (one per cent). Both series were given 200 mg. of KI by stomach tube every other day for seven days. Two additional series of rats were given the same two diets without KI administration for control purposes. At the end of seven days, the animals were sacrificed and the liver was obtained. Plasma samples obtained at the beginning and end of the experiment were analyzed for cholesterol and total lipid. The liver was analyzed for cholesterol.

The chronic effect of KI was studied by administering 200 mg. of KI every other day for 21 days to one of two series of rats ingesting Purina chow enriched with cholesterol (two per cent) and cholate (two per cent). Plasma samples obtained at the beginning and end of

TABLE II
The effect of KI on absorption of cholesterol in the rabbit

No. of rabbits	Average weight gm.	Intestinal excretion—72 hours			Non-cholesterol sterol mg./72 hrs.
		Dry weight gm.	Total sterol mg./72 hrs.	Total cholesterol mg./72 hrs.	
Control rabbits given 800 mg. of cholesterol					
16	1,436	35.9	463	352	110
	Range: (1,190–1,749)	(20.0–47.9)	(125–777)	(110–577)	(28–309)
	S.E. Mean:		±51	±36	±25
Rabbits given 800 mg. of cholesterol + 1,250 mg. of KI					
10	1,424	35.1	475	363	105
	Range: (1,310–1,645)	(23.6–47.0)	(196–833)	(150–603)	(27–230)
	S.E. Mean:		±58	±48	±19

the experiment were analyzed for cholesterol and total lipids.

B. *Rabbits*: The acute effect of KI upon plasma cholesterol and total lipid of the rabbit was studied by giving in one dose, 1250 mg. of KI by stomach tube to half of a group of 20 rabbits that also were given 800 mg. of cholesterol in 8 ml. of olive oil. Plasma samples obtained before and 72 hours after the administration of the cholesterol were analyzed for plasma cholesterol.

The chronic effect of KI was studied by placing 20 rabbits upon a high cholesterol diet consisting of ground stock rabbit pellets together with added cholesterol (0.5 per cent) and potassium iodide (0.25 per cent). A control series of 20 rabbits was given the same diet except potassium chloride was substituted for the iodide. It was calculated that these rabbits ingested approximately 300 mg. of cholesterol and 150 mg. of KI per day during the 21 days of feeding. Plasma samples obtained before and seven, 14 and 21 days after the beginning of the diet were analyzed for cholesterol and total lipid.

Results

A. *Rats*: Whether rats were ingesting a stock diet or the cholesterol enriched diet, the adminis-

tration of KI in the dosage employed appeared to effect acutely a slight but apparently a significant rise in the plasma cholesterol at the end of the seven-day period (see Table IV, Sections I and II). This hypercholesteremic effect of KI has been reported previously (15). The plasma lipid concentration however did not appear to be affected by the administration of KI.

The administration of KI for 21 days however to rats ingesting an hypercholesteremia-inducing diet appeared to have little or no effect upon either their plasma cholesterol or total lipid (see Table IV, Section III).

B. *Rabbits*: The administration of a single dose of 1250 mg. of KI did not appear to have any effect upon the acute hypercholesteremia occurring in rabbits given a single dose of 800 mg. of cholesterol. The average plasma cholesterol of the 10 rabbits given the single dose of cholesterol and iodide was 78 before and 252 mg. per 100 ml.

TABLE III
The effect of KI on excretion of cholesterol in the rat

No. of rats	Average weight gm.	Intestinal excretion—72 hours			Non-cholesterol sterol mg./72 hrs.
		Dry weight gm.	Total sterols mg./72 hrs.	Total cholesterol mg./72 hrs.	
Control rats given 3 ml. of olive oil					
5	233	2.3	29.8	15.1	14.7
	Range: (228–246)	(1.8–2.8)	(23.1–34.0)	(9.5–19.5)	(12.0–21.0)
	S.E. Mean:		±1.7	±1.7	±1.4
Rats given 3 ml. of olive oil + 200 mg. of KI					
5	248	2.0	32.3	12.9	19.4
	Range: (232–266)	(1.6–2.9)	(21.4–47.6)	(9.7–16.4)	(12.0–31.2)
	S.E. Mean:		±4.1	±1.2	±3.0

(S.E. Mean \pm 19) 72 hours later. Comparable values obtained in the 10 rabbits given only the cholesterol were 81 and 286 mg. per 100 ml. (S.E. Mean \pm 36), respectively.

The chronic administration of KI to rabbits was found to diminish the food intake of nine of the 20 rabbits and in such rabbits, a slight fall in weight occurred. A similar lessened food intake and fall in weight occurred in only three of the 20 control rabbits receiving KCl in their cholesterol enriched diet. For purposes of comparison, therefore, cholesterol and lipid values obtained from the rabbits who ate well and gained weight in each series were tabulated separately from those who failed to do so.

As Table V demonstrates, those rabbits ingesting KI in their high cholesterol diet who both ate well and gained weight, exhibited as great an increase in their cholesterol and total lipid content as was observed in the control rabbits that gained weight while ingesting KCl. On the other hand, far less hypercholesteremia and hyperlipemia were observed in the nine rabbits fed iodide and the three control rabbits fed chloride that ate poorly and lost weight in the three-week period. (See Table V, Sections I-B and II-B.)

IV. *The Effect of Potassium Iodide Upon Biliary Excretion of Cholesterol*

Methods

Ten male Long-Evans rats (average weight: 194 grams) were placed upon a sterol free diet for 72 hours. In addition, five of these rats were given 200 mg. of KI in one ml. of H₂O by stomach tube daily. Immediately following the last administration of KI, all of the rats then were anesthetized with ether, the abdomen incised and the bile duct cannulated and bile was collected for 24 hours. The bile samples were analyzed for total cholesterol. The methods employed both for the cannulation and the cholesterol analysis of the bile have been previously described (16).

Results

The volume of bile as well as its total cholesterol content was essentially the same in both the iodide treated and control animals. The average volume of bile excreted was 14.5 ml. per 24 hrs. (Range: 11.0 to 16.8 ml.) in the iodide treated and 14.6 ml. per 24 hrs. (Range: 13.0 to 16.3 ml.) in the control animals. The average total cholesterol ex-

creted in 24 hours was 1.42 mg. (Range: 1.07 to 1.58) in the former and 1.35 mg. (Range: 0.97 to 1.61) in the latter group of animals. This observed failure of iodide to alter the biliary excretion of cholesterol suggests that no change in the hepatic rate of synthesis of cholesterol (17) is mediated by iodide ingestion.

V. *The Effect of Potassium Iodide Upon Various Endogenous Types of Hypercholesteremia*

A. Hypercholesteremia Induced by Intravenous Injection of Hypercholesteremic Serum

Methods

Two series of male Long-Evans rats were placed upon a sterol free diet for 72 hours during which time they were given 200 mg. of KI daily by stomach tube. Immediately after the last iodide feeding, the first series (15 rats) was injected intravenously with 20 mg. of cholesterol in the form of pooled hypercholesteremic serum (3 ml.) previously obtained from cholate fed, bile obstructed rats (18). The second series (10 rats) was given 20 mg. of cholesterol in the form of pooled hypercholesteremic serum (2.5 ml.) previously obtained from cholesterol fed rabbits. Two control series of rats also on the sterol free diet but receiving no iodide were also injected with the two types of sera, respectively. Plasma samples obtained prior to and then immediately, six, 12 and 24 hours after the injection of the hypercholesteremic sera were analyzed for cholesterol.

Results

As previously observed, administration of iodide (prior to injection of rat hypercholesteremic serum) alone elevated the average plasma cholesterol of the first series from 49 (S.E. Mean \pm 2.1) to 92 mg. per 100 ml. (S.E. Mean \pm 5.4) whereas the control series exhibited an average plasma cholesterol of 42 (S.E. Mean \pm 2.8) before and 65 mg. per 100 ml. (S. E. Mean \pm 3.7) 72 hours after being placed upon the sterol free diet. When the rat hypercholesteremic serum was given to the experimental and control series, both groups became immediately hypercholesteremic but the pre-injection divergence in values was maintained (see Figure 1). The rate of disappearance of the excess plasma cholesterol however proceeded at approximately the same rate (see Figure 1) in the iodide and control series, respectively. A similar train of events was observed in the iodide treated and control series given rabbit hypercholesteremic serum (see Figure 1).

TABLE IV
The acute and chronic effect of KI on plasma cholesterol, lipid and hepatic cholesterol of the rat given various diets

No. of rats	Average weight gm.	Plasma cholesterol (mg./100 ml.)		Plasma lipid (mg./100 ml.)		Liver (after 7 days)		
		Before	7 days	Before	7 days	Dry weight	Cholesterol mg./100 g. total mg./organ	
I. Stock diet								
A. Control rats								
17	Range: S.E. Mean: 225 (188-256)	65 (46-80) ±2.6	59 (45-71) ±2.3	242 (162-309)	200 (117-279)	2.99 (2.1-3.9)	795 (653-910) ±42	23.6 (18.4-30.9) ±0.8
B. Rats given 200 mg. of KI every other day								
17	Range: S.E. Mean: 216 (198-224)	62 (51-82) ±2.1	72 (57-102) ±2.3	264 (197-338)	185 (133-276)	2.58 (2.1-3.3)	950 (692-1,720) ±60	24.8 (15.3-45.0) ±1.7
II. Stock diet + 1% cholesterol								
A. Control rats								
17	Range: S.E. Mean: 212 (196-230)	52 (30-66) ±2.3	59 (40-74) ±2.1	204 (136-273)	212 (173-291)	3.07 (2.3-3.8)	1,407 (950-2,530) ±106	43.1 (28.0-81.6) ±3.5
B. Rats given 200 mg. of KI every other day								
14	Range: S.E. Mean: 219 (194-248)	59 (46-76) ±2.4	79 (60-126) ±4.3	205 (130-409)	206 (119-409)	2.62 (1.8-3.5)	1,483 (846-2,730) ±130	38.4 (19.9-63.5) ±3.3
III. Stock diet + 2% cholesterol + 2% cholate								
A. Control rats								
14	Range: S.E. Mean: 291 (242-290)	58 (47-67) ±2.4	131 (99-202) ±7.0	243 (124-187) ±23	259 (204-339) ±10			
B. Rats given 200 mg. of KI every other day								
12	Range: S.E. Mean: 243 (212-290)	59 (48-69) ±2.1	150 (91-262) ±17	250 (159-327) ±14	290 (207-361) ±15			

TABLE V
The chronic effect of KI on plasma cholesterol and lipid of rabbits on high cholesterol diet

No. of rabbits	Average weight (gm.)		Plasma cholesterol (mg./100 ml.)			Plasma total lipid (mg./100 ml.)			
	Before	21 days	Before	7 days	14 days	21 days	Before	21 days	
I. Control rabbits given KCl									
A. Rabbits gaining weight									
17	Range: S.E. Mean:	1,898 (1,685-2,665)	2,066 (1,760-2,885)	58 (46-74) ±2.1	184 (92-327) ±25	281 (67-474) ±76	284 (81-984) ±62	204 (149-363) ±17	553 (145-188) ±119
B. Rabbits losing weight									
3	Range:	1,697 (1,610-1,795)	1,577 (1,500-1,710)	54 (48-59)			97 (79-120)	170 (61-281)	303 (140-428)
II. Rabbits given KI									
A. Rabbits gaining weight									
11	Range: S.E. Mean:	1,964 (1,765-2,190)	2,024 (1,810-2,365)	63 (49-87) ±2.1	215 (114-417) ±36	271 (194-715) ±73	340 (120-943) ±71	236 (154-356) ±25	680 (264-1,935) ±160
B. Rabbits losing weight									
9	Range: S.E. Mean:	1,846 (1,590-2,105)	1,728 (1,670-1,990)	62 (32-91) ±2.3	118 (77-168) ±24	119 (85-156) ±25	149 (65-402) ±32	217 (88-307) ±21	397 (187-918) ±84

The results of both these experiments left little doubt that iodide administration while elevating the average plasma cholesterol slightly did not alter the rate of disappearance of injected cholesterol when it was administered in physiological form.

B. Hypercholesteremia Induced by Biliary Obstruction and by Injection of Triton

Methods

Thirty-two male Long-Evans rats (average weight: 246 grams) were subjected to ligation of their biliary duct immediately after 15 of the rats were given 200 mg. of KI by stomach tube. Plasma samples obtained before and 24 hours after the ligation were analyzed for total cholesterol and total lipid.

A series of 20 male Long-Evans rats (average weight: 274 grams) were injected intravenously with 100 mg. of Triton WR-1339⁸ after half of the animals were given 200 mg. of KI by stomach tube. Plasma samples obtained before and 24 hours after the injection were analyzed for total cholesterol and total lipid.

Results

The hypercholesteremia and hyperlipemia resulting after biliary obstruction was not altered by the acute administration of KI (see Table VI).

Similarly, the hypercholesteremic and hyperlipemic effect of injected Triton was not altered by acute administration of KI (see Table VI).

VI. The Effect of Potassium Iodide Upon the Atherosclerosis of the Cholesterol Fed Rabbit

Methods

Two series of feeding experiments were carried out successively. In the first series, 10 of a group of 20 male albino rabbits (average weight: approximately 2,000 grams) were placed upon a diet consisting of ground rabbit pellets containing 3.5 mg. of cholesterol dissolved in 0.1 ml. of olive oil, plus 1.75 mg. of KI, per gram of pellet mixture. The remaining 10 rabbits serving as controls received the identical mixture except that KCl was substituted for KI. The daily food consumption of each group of rabbits was measured daily and the weights of the animals were obtained every three weeks. Blood samples obtained prior to, and then three, six, nine, 12 and 15 weeks after institution of the special cholesterol-cation diet, were analyzed for total cholesterol and total lipids. At the end of 15 weeks, the animals were sacrificed

⁸ A para-isooctyl polyoxyethylene phenol polymeric detergent kindly furnished by Rohm and Haas Co., Philadelphia, Penna.

THE EFFECT OF POTASSIUM IODIDE UPON RATE OF DISAPPEARANCE OF TWO TYPES OF INJECTED HYPERCHOLESTEREMIC SERUM

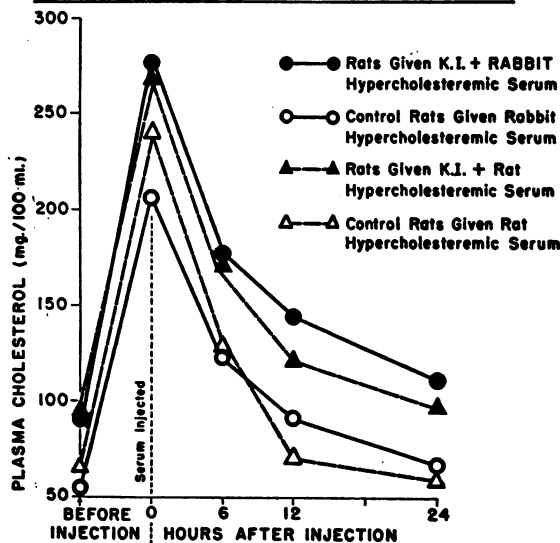


FIG. 1. THE EFFECT OF POTASSIUM IODIDE UPON RATE OF DISAPPEARANCE OF TWO TYPES OF INJECTED HYPERCHOLESTEREMIC SERUM

and their aortas were examined and graded (0 to 4) for the presence of atherosclerosis.

The second series of 20 rabbits was begun after the termination of the study of the first series. Because a marked difference in food consumption between the two groups of the first series had been observed the two groups of rabbits of the second series were pair fed although each group received one of the two cholesterol-cation enriched diets described above. The weights of the animals were obtained monthly. Blood samples obtained prior to and then four, 12 and 16 weeks after institution of the diet were analyzed for total cholesterol and lipid. The animals were sacrificed at 16 weeks and besides gross estimation of the degree of aortic atherosclerosis, a segment of the entire aorta (consisting of the first 5 cm. of its length from the aortic cusps) was obtained and analyzed for total cholesterol content.

Results

First series. Nine of the rabbits fed KI and six of the rabbits fed KCl survived the experimental period of 15 weeks. The death of the remainder appeared to be due to cardiac tamponade following blood sampling. It was observed that although both groups of rabbits gained about equally during the 15-week period, the rabbits fed iodide approximately three weeks after being on the diet, ingested 20 to 40 per cent less of the food than did the animals fed KCl, again exhibiting the de-

TABLE VI

The effect of KI on hypercholesteremic effects of (a) biliary obstruction and (b) Triton injection in the rat

No. of rats	Average weight gm.	Plasma cholesterol (mg./100 ml.)		Plasma lipid (mg./100 ml.)	
		Before	24 hours	Before	24 hours
I. Rats subjected to ligation of bile duct					
A. Control rats subjected to ligation only					
17	247 Range: (190-306) S.E. Mean:	55 (46-56) ±2.1	140 (100-184) ±5.9	181 (163-185) ±7.7	336 (228-470) ±47.0
B. Rats subjected to ligation and given KI					
15	245 Range: (193-310) S.E. Mean:	55 (44-66) ±2.0	152 (108-200) ±6.9	210 (206-214) ±2.0	342 (188-412) ±46.0
II. Rats injected with Triton					
A. Control rats injected with Triton only					
10	278 Range: (200-304) S.E. Mean:	59 (48-69) ±2.3	415 (336-489) ±12	191 (112-302) ±18	2,695 (1,638-3,880) ±187
B. Rats injected with Triton and given KI					
10	269 Range: (198-308) S.E. Mean:	56 (42-85) ±2.4	362 (204-477) ±24	172 (103-302) ±55	2,615 (1,853-4,960) ±870

laid anorectic propensity of iodide ingestion previously noted. Thus, whereas the average daily consumption of the two groups was 93 and 94 grams per day, respectively, during the first three weeks, the average daily ingestion of the rabbits fed KCl increased to 218 grams per day from the third to the 15th week whereas the ingestion of the rabbits fed KI increased only to 158 grams per day. This difference in ingestion of course meant that the rabbits fed KCl were obtaining an average of 763 mg. of cholesterol and 382 mg. of KCl per day as compared to the 553 mg. of cholesterol and 276 mg. of KI per day ingested by the rabbits fed iodide. Despite this difference in intake, however, there was little difference in the average weights of the two groups at the end of 15 weeks. Thus the initial average weights of the KI and KCl groups were 1,792 and 1,789 grams, respectively, and at the end of the 15 weeks, their average weights were 3,344 and 3,419 grams, respectively. In other words, the difference in food intake of the two groups could not have been detected by mere measurement of the body weight of the two groups.

Although the average plasma cholesterol of the rabbits fed KI increased during the feeding period from 60 (Range: 31 to 86) to 1,048 mg. per 100

ml. (Range: 635 to 1,500) at the end of the 15-week period, the plasma cholesterol after the third week was consistently less than that observed in the rabbits fed KCl. It should be observed nevertheless that at the end of the feeding period, the average plasma cholesterol of the rabbits fed KI had reached a marked hypercholesteremic level. The average plasma cholesterol of the group fed KCl increased from 55 (Range: 37 to 72) to 1,327 mg. per 100 ml. (Range: 1,010 to 1,525) during the same period. The plasma total lipid content of the two groups similarly differed. Thus the average plasma lipid of the rabbits fed KI was 223, 421, 393, 513, 891 and 1,362 mg. per 100 ml. at the beginning and after three, six, nine, 12, and 15 weeks, respectively, of the feeding program. The average plasma lipid of the rabbits fed KCl was 182, 398, 248, 874, 1,219, and 1,622 mg. per 100 ml., respectively, at similar periods.

The divergency in plasma cholesterol and total lipid between the two groups was reflected in the incidence and degree of atherosclerosis found in the aorta. Thus five of the nine rabbits fed KI exhibited no gross atherosclerosis whereas each of the six rabbits fed KCl had some aortic atherosclerotic infiltration. Judged on the scale of one

to four, the average degree of atherosclerosis was 1.2 (Range: 0 to 3.0) in the rabbits fed KI and 2.5 (Range: 1 to 4) in the rabbits fed KCl.

Second series. As Table VII demonstrates, when the intake of food and cholesterol was kept exactly the same in the rabbits fed KI and KCl the increases in the average plasma cholesterol and total lipid were approximately the same in the two series during the entire feeding period.

The findings in the aorta also were essentially similar in the two series. On gross inspection, eight of the 10 rabbits fed KI and six of the eight rabbits fed KCl exhibited aortic atherosclerosis. The average degree of deposition was judged to be 1.7 (Range: 0 to 4.5) in the rabbits fed KI and 1.8 (Range: 0 to 4.0) in the rabbits fed KCl. The average cholesterol content of the aortas of the two groups also was approximately the same being 1,528 mg. per 100 grams of aorta in the rabbits fed KI and 1,730 in the animals fed KCl. Calculation of the Standard Error of the Difference of Means indicates that a good agreement exists between the two values. When sections of aortas of each group were stained with Sudan IV and examined microscopically, no difference could be observed in either the intimal hyperplasia or the deposition of lipid in the aortas of either group.

DISCUSSION

Except for a moderate acute and temporary hypercholesteremia (15), the administration of potassium iodide was not found in these studies to have any significant, specific effect upon the intestinal absorption or excretion of cholesterol nor upon its endogenous disposition, including the plasma level of cholesterol.

The results obtained in our first series of rabbits given KI plus cholesterol in their diet appeared to indicate that unless special measures were taken, such rabbits became initially anorectic, hence ingested less cholesterol and as a consequence exhibited a lower plasma cholesterol and less atherosclerosis than the control animals. However when the control rabbits of the second series were not allowed to ingest any more food and cholesterol than that taken up by the rabbits fed iodide, no differences in plasma cholesterol and atherosclerosis were observed between the rabbits fed iodide and those given chloride.

The divergency observed in the degree of hy-

TABLE VII
The effect of KI on atherosclerosis occurring in cholesterol fed rabbits

No. of rabbits	Average weight		Average plasma cholesterol (mg./100 ml.)				Plasma lipid (mg./100 ml.)				Aorta	
	Beginning	16 weeks	Beginning	8 weeks	12 weeks	16 weeks	Beginning	8 weeks	12 weeks	16 weeks	Atherosclerosis (1-5)	Cholesterol content mg./100 gm.
10	2,269	3,096	40	324	687	876	588	588	1,313	1,706	1.7	1,528
	(2,090-2,520)	(2,800-3,687)	(21-71)	(109-517)	(415-1,100)	(414-1,020)	(136-228)	(414-945)	(820-1,775)	(1,165-2,490)	(0.0-4.5)	(900-2,623)
8	2,405	3,209	47	337	866	805	462	462	1,073	1,735	1.8	1,730
	(2,170-2,595)	(2,683-3,553)	(33-64)	(75-906)	(202-1,490)	(232-1,020)	(128-570)	(140-1,220)	(315-1,783)	(401-2,860)	(0.0-4.0)	(875-2,525)
3	2,337	3,192	66	69	184	184	184	184	200	200	0	>714
	(2,250-2,595)	(3,065-3,261)	(62-70)	(50-70)	(128-240)	(128-240)	(128-240)	(128-240)	(190-220)	(190-220)	0	(661-776)

A. Rabbits getting KI plus cholesterol

B. Rabbits getting KCl plus cholesterol

C. Control rabbits on stock diet

percholesteremia, hyperlipemia and aortic atherosclerosis between our two series appears to us to furnish a probable explanation why so many earlier investigators believed iodide was an anti-hypercholesteremic and anti-atherogenic agent. Their studies were done upon rabbits ingesting cholesterol-containing food at will and seemingly iodide administration depresses such food intake markedly after a few weeks. Since the appetite of the control rabbits was not similarly affected, the degree of hypercholesteremia and consequent atherosclerosis obviously became more marked in the latter at least during the first 15 weeks of feeding. However the cholesterol level in the blood of even the first series of rabbits fed KI was becoming high enough to be compatible with the eventual deposition of cholesterol in the aorta. This last observation perhaps explains the later observation of Turner and Bidwell (9) that the effect of iodide administration in rabbits fed cholesterol was lost after a few months.

SUMMARY

In a study employing both the rat and rabbit, the administration of iodide was not found to alter the intestinal absorption or excretion of cholesterol. Further, except for a slight initial hypercholesteremic effect in the rat, iodide administration was not found to alter either the normal or abnormal disposition of endogenous cholesterol. Similarly it was not found to alter the hypercholesteremic response of the rat to cholesterol enriched food or that of the rabbit (if allowance were made in this animal for the delayed anorectic effect of iodide administration).

Rabbits given iodide and a high cholesterol diet exhibited as much aortic atherosclerosis and cholesterol deposition as control rabbits when special measures were taken to ensure equal intake of a cholesterol enriched diet.

REFERENCES

- Liebig, H., Experimentelle Untersuchungen über die Jodwirkung auf die Atherosklerose. *Med. Klin.*, 1929, 25, 1100.
- Liebig, H., Die Beeinflussung der experimentellen Atherosklerose durch Jodbehandlung. *Arch. f. exper. Path. u. Pharmakol.*, 1931, 159, 265.
- Turner, K. B., Studies on the prevention of cholesterol atherosclerosis in rabbits. I. The effects of whole thyroid and potassium iodide. *J. Exper. Med.*, 1933, 58, 115.
- Turner, K. B., and Khayat, G. B., Studies on the prevention of cholesterol atherosclerosis in rabbits. II. The influence of thyroidectomy upon the protective action of potassium iodide. *J. Exper. Med.*, 1933, 58, 127.
- Ungar, H., Zur Wirkung des Jods auf die Cholesterin-Atheromatose der Kaninchen. *Arch. f. exper. Path. u. Pharmakol.*, 1934, 175, 536.
- Breusch, F., and Thiersch, H., Der Einfluss des Jods auf die Kaninchenatheromatose. *Ztschr. f. d. ges. exper. Med.*, 1935, 95, 458.
- Rosenthal, S. R., Studies in atherosclerosis: Chemical, experimental and morphologic. V. Possible dangers of iodine therapy in atherosclerosis of aorta seen from an experimental standpoint. *Arch. Pathol.*, 1934, 18, 827.
- Page, I. H., and Bernhard, W. G., Cholesterol-induced atherosclerosis. Its prevention in rabbits by the feeding of an organic iodine compound. *Arch. Pathol.*, 1935, 19, 530.
- Turner, K. B., and Bidwell, E. H., Further observations on the blood cholesterol of rabbits in relation to atherosclerosis. *J. Exper. Med.*, 1935, 62, 721.
- Turner, K. B., and Bidwell, E. H., Some effects of iodine given to rabbits after a brief period of cholesterol feeding. *Proc. Soc. Exper. Biol. & Med.*, 1937, 35, 656.
- Brown, H. B., and Page, I. H., The effect of oral iodide on serum butanol-insoluble protein-bound iodine in various species. *Circulation*, 1954, 10, 714.
- Byers, S. O., Friedman, M., and Gunning, B., Observations concerning the production and excretion of cholesterol in mammals. XI. The intestinal site of absorption and excretion of cholesterol. *Am. J. Physiol.*, 1953, 175, 375.
- Saifer, A., and Kammerer, O. F., Photometric determination of total cholesterol in plasma or serum by a modified Liebermann-Burchard reaction. *J. Biol. Chem.*, 1946, 164, 657.
- Bragdon, J. H., Colorimetric determination of blood lipides. *J. Biol. Chem.*, 1951, 190, 513.
- Homer, R. S., Effect of potassium iodide on plasma cholesterol of rats. *Proc. Soc. Exper. Biol. & Med.*, 1955, 88, 354.
- Friedman, M., Byers, S. O., and Michaelis, F., Observations concerning production and excretion of cholesterol in mammals. II. Excretion of bile in the rat. *Am. J. Physiol.*, 1950, 162, 575.
- Byers, S. O., and Friedman, M., Production and excretion of cholesterol in mammals. VII. Biliary cholesterol; increment and indicator of hepatic synthesis of cholesterol. *Am. J. Physiol.*, 1952, 168, 297.
- Friedman, M., Byers, S. O., and Gunning, B., Observations concerning production and excretion of cholesterol in mammals. VIII. Fate of injected cholesterol in the animal body. *Am. J. Physiol.*, 1953, 172, 309.